AMERICAN
SOCIETY of
GENE
THERAPY

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The ASGT appreciates the opportunity to comment on the "Challenge and Opportunity on the Critical Path to new Medical Products" statement developed by the U.S. Food and Drug Administration (March 2004). The document addresses a variety of key issues that directly impact the development of novel therapies. While the Society believes there are additional factors that should be considered in developing the ***Critical Path*** initiative, the document presented is an excellent overview of existing problems and we support the efforts outlined in the proposal.

ASGT offers to assist, as a Society or through its members, in the development of the ***Critical Path Opportunities List***. As we have in the past, our members will be available to provide scientific guidance in the development of new processes, reference standards, and scientific review or advice. We agree that the time is right for a re-evaluation of the product approval methods, assessment, and review. We also concur that a major focus of these changes should be the improvement of the safety profile for medical products at all stages of product development, as well as patients utilizing these products after licensure.

While ASGT is supportive of the goals proposed in the ***Critical Path*** document, the paper does raise a number of additional considerations that the Society believes should be addressed to maximize the success of this initiative.

A major concern for all those involved with product development is the decrease in IND applications over the past several years. While the reason may be regulatory hurdles that the FDA can influence through this initiative, there may be other factors that could be responsible. For example, ASGT members have anecdotal data that there is continued interest in conducting clinical gene therapy trials but biotechnology companies are seeking to conduct these studies abroad. If this proves to be the case, then the ***Critical Path*** may take a distinctly different direction in addressing the decrease in IND submission. Also, a decrease in IND submissions may relate to liability concerns on the part of industry, hospitals and academic institutions. For one example, while state universities generally believe that sovereign immunity protects them from product liability suits such as might be attached to a gene vector in a clinical program, many other academic institutions and hospitals are at potential risk and that can be a disincentive. If this is found to be a significant barrier to product development, this issue should be incorporated into the ***Critical Path*** initiative.

2004N-0181 C 15

Another area that requires exploration is the role of insurance providers in the conduct of clinical trials. The majority of current insurance providers do not cover the cost of investigational therapies and NIH grants typically cover only a modest percentage of the total cost of a clinical trial. This leaves significant costs to be borne by the combined efforts of industry, hospitals, and academic institutions. As the available funds within academic institutions and hospitals have decreased over the past decade, the resources required to conduct investigational trials have become limited. The anticipated decrease in the NIH budget suggests that additional limitations may be placed on clinical trials resources.

One strategy to improve the process of new protocol review and ongoing protocol supervision would be to create a new kind of expert advisory panel to fill a gap between the existing advisory committees and the FDA staff. At the present time, the advisory committees such as the BRMAC for gene therapy in CBER, review large challenges facing product development such as long term follow-up, safety of retroviral gene therapy and objective clinical measures for safety and efficacy. However, once a specific proposal begins the process of FDA review, approval, clinical implementation and oversight, there is no path for sponsors in industry or academic institutions except to go directly back to the FDA staff to raise or resolve concerns about specific demands, limitations, delays or any other kind of critical process problem. We suggest that one way to address this issue would be to create an outside expert panel that would specifically review any kind of sponsor-initiated concern and make recommendations back to FDA leadership regarding potential resolutions.

The document put forth by the FDA suggests more inclusion of patients in assessing the value of their health care dollars. This assessment should go beyond assessing drug efficacy, it should include a critical understanding of the drug development process given its cost and potential impact on the total health care costs. An area that should be evaluated carefully is the information presented in Figure 1: "10-Year Trends in Biomedical Research Spending". This Figure demonstrates increasing resources committed to R&D by the pharmaceutical companies, implying a future of new and advanced therapies. Understanding how the money is actually directed may be informative. Are significant new resources spent in developing novel therapies or were much of the resources used to protect existing market share or to develop "me too" drugs? Bringing an allergy medication to market that can be taken once a day as opposed to twice a day is unlikely to be cost-effective from a health policy point of view but may prove financially profitable if the prior formulation goes off patent. Likewise, a number of companies have developed derivative drugs (ex. drugs for erectile dysfunction) that may have consumed a substantial part of the industry's R&D budget. Finally, it will be important to consider the diseases for which drugs are being developed. From the perspective of patients, families and health care providers, the size of a potential market in dollars cannot be the only metric to determine where R&D investment is made. As development of the ***Critical Path*** will deal with health policy issues, there is an opportunity to consider how R&D investment can be refined to better reflect our nation's health care needs.

The Society agrees enthusiastically with the development and publication of guidance documents which traditionally provide important direction, particularly in the development of novel products. However, there is concern about the length of time that is generally required for the publication of such documents and the ***Critical Path*** should address ways in which resources can

be provided to the FDA to develop these documents in a timely manner. As importantly, working to keep current Guidance documents as up-to-date as possible will be another important goal for facilitating product development.

The Society also agrees with the statement that the "challenges involved in successful industrialization are complex, though highly underrated in the scientific community". This is a critical point in development of gene therapy products, which are often developed initially in the context of academic centers or "start-up" companies. As pointed out, funding agencies have not traditionally viewed process development and novel assessment methods within their mandate. Nevertheless, if academia is to continue to play a role in product development and early stage testing, more resources will be required in this area.

One of the greatest concerns for members of the Society is the availability of resources to the FDA, particularly the Office of Cellular, Tissue and Gene Therapies. To date, CBER and the Office have provided exceptional service to our Society and its members in the form of education, guidance, and willingness to address key issues that have faced our field. Nevertheless, we also realize the challenges faced by the development and implementation of the ***Critical Path*** initiative. We are concerned that adequate personnel and financial resources may not be available for this substantial development program. We hope that the FDA would assess the potential impact of this initiative on the existing review process, taking advantage of internal and external advisors. As part of this assessment, the ASGT hopes the FDA will also evaluate the workload of existing personnel. Mechanisms to foster retention, as well as systems that maximize consistency in Agency recommendations as key personnel changes, would provide added value to the ***Critical Path*** endeavor. We also strongly support the research activities of CBER scientists, an effort that creates "in house" expertise in many areas directly relevant to new product development that is invaluable to both sponsors and the public. However, we have watched a steady erosion of budget support for science within the FDA that reflects current fiscal realities. We would hope that support for science can increase in the future and suggest that this objective be incorporated into the ***Critical Path***.

What is unresolved and requires further discussion is where the efforts envisioned in the current document would be performed. Specifically, would the FDA seek to conduct much of the research for process development and assessment in house, through grants to academia and industry, or by working through other government agencies to increase funding for this work? The Society is concerned that significant re-budgeting of existing FDA funds would divert efforts from an Office which is charged with a broad portfolio during a critical time in the developing field of gene therapy.

Finally, given the various issues highlighted above, including the need for increased funding for process development and assessments, along with legal and financial barriers to clinical trials, ASGT believes an inclusive effort from federal agencies, industry and academia will be required for the successful development and implementation of this important initiative. ASGT is in an excellent position to solicit and present key product development hurdles facing a wide variety of stakeholders and will be willing to assist the FDA as it moves forward in this endeavor.

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